

Erythema multiforme-like lesions in children and COVID-19

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ABSTRACT

During examination of cases of chilblains in children and adolescents, we identified four patients who also showed skin lesions similar to erythema multiforme (EM). They had no other known triggers for EM. One of them had a positive PCR for SARS-CoV-2, while the other 3 were negative. Skin biopsies from two patients showed features not typical of EM, such as deep perivascular and perieccrine infiltrate and absence of necrosis of keratinocytes. Immunohistochemistry for SARS-CoV/SARS-CoV-2 spike protein showed granular positivity in endothelial cells and epithelial cells of eccrine glands in both biopsies. All patients had an excellent outcome, and had minimal or no systemic symptoms. The coincidence of EM, a condition commonly related to viruses, and chilblains in the setting of COVID-19, as well as the positivity for SARS-CoV/SARS-CoV-2 spike protein by immunohistochemistry strongly suggest a link between EM-like lesions and SARS-CoV-2.

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other known triggers for EM. One of them had a positive PCR for SARS-CoV-2, while the other 3 were negative. Skin biopsies from two patients showed features not typical of EM, such as deep perivascular and perieccrine infiltrate and absence of necrosis of keratinocytes. Immunohistochemistry for SARS-CoV/SARS-CoV-2 spike protein showed granular positivity in endothelial cells and epithelial cells of eccrine glands in both biopsies. All patients had an excellent outcome, and had minimal or no systemic symptoms. The coincidence of EM, a condition commonly related to viruses, and chilblains in the setting of COVID-19, as well as the positivity for SARS-CoV/SARS-CoV-2 spike protein by immunohistochemistry strongly suggest a link between EM-like lesions and SARS-CoV-2.

KEY WORDS: SARS-CoV-2, COVID-19, skin, chilblain, pernio, erythema multiforme.

Introduction

Skin manifestations including urticarial, morbilliform, vesicular and petechial exanthems, and vasospastic manifestations such as livedo reticularis and acral ischemic lesions (1-5) have been reported in association with coronavirus disease 2019 (COVID-19). In particular, chilblains on the feet and hands have been extensively documented worldwide during the peak incidence of the pandemic (6-8). During our examination of 22 cases of chilblains in children and adolescents (9) we identified four patients who also showed skin lesions similar to erythema multiforme. We report these cases and discuss their clinical and histopathologic features, as well as the possible relationship to COVID-19.

Case reports

The four children (3 male, 1 female; age 11-17 years) had been referred from the emergency department as part of a study to record acral skin lesions during the peak period of incidence of COVID-19 in Madrid, Spain (9). Clinical examination confirmed chilblains on the feet (four cases) and also on the hands (two cases). In addition, complete examination disclosed different skin lesions involving the hands, feet, forearms, elbows, arms, ankles, legs, thighs and ears (Table 1). They consisted of target (three rings) and targetoid (two rings), confluent macules, papules and plaques, with different sizes, some with hemorrhage

or a small central crust (Figures 1 and 2). Three patients complained of itch, and mild pain in the lesions was noted by one of them.

None of the patients had a previous history of erythema multiforme. A recent lip sore was not recalled, and no patient had been taken any new drug or had been vaccinated within 30 days before the onset of the skin lesions. One patient was on treatment with methylphenidate at the same dose for more than one year. SARS-CoV-2 PCR from oropharyngeal and nasopharyngeal swabs was performed in all the cases, and only one was positive. Routine hematological and biochemical analyses were normal, when done.

Skin biopsies were taken in two cases (Figure 3). Histopathology revealed a relatively normal epidermis lacking parakeratosis or hyperkeratosis. Spongiosis and mild vacuolar interface damage and exocytosis of lymphocytes were seen, being moderate in one case and mild in the other. Necrotic keratinocytes were absent in both samples. A superficial and deep perivascular and perieccrine lymphocytic infiltrate reaching the adipose tissue was noted, which was mild in one case and moderate in the other one. No eosinophils were seen in the infiltrate. Vascular ectasia and mild features of lymphocytic vasculitis were observed, but fibrinoid necrosis and thrombosis were absent.

Immunohistochemistry showed similar results in both cases. The inflammatory infiltrate was mainly composed by CD3+ T cells, with a mix of CD4+ and CD8+ populations (CD4 predominant). Scattered B cells were present (CD20+ and CD79a+) as well as very few CD30+ cells. Immunohistochemical stain with the antibody against SARS-CoV/SARS-CoV-2 spike protein (clone 1A9, GeneTex, California, USA) showed granular positivity in endothelial cells and epithelial cells of eccrine glands in both cases (Figure 4)

One patient was given a short course of oral corticosteroids and another patient received topical corticosteroids. All patients experienced complete remission of their skin lesions within one to three weeks and had no complications.

Discussion

We present four patients with lesions clinically consistent with erythema multiforme (EM) and histopathological features not specific or typical for EM. These lesions were located on the most common cutaneous sites of involvement of classical EM. They appeared in patients with COVID-19-related chilblains, similar to those extensively described in social networks in

most countries affected by the pandemic, and also in medical journals (6-9). The outbreak of these acral ischemic lesions, very rarely seen before in children and adolescents, coinciding with the peak incidence of COVID-19, strongly suggest a causal role for SARS-CoV-2. In patients with chilblains the rate of positivity for SARS-Cov-2 PCR has been consistently very low (8,9), a reason why some authors have argued against a viral causality.

The presence of EM lesions in adolescents with chilblains in the setting of COVID-19 has been rarely reported (10), but may have been overlooked, possibly because chilblains in case series were reported via photographs and may have not been seen in an ideal clinical setting by dermatologists. One report describes “erythematopapular targetoid lesions on the hands and elbows after few days” (10) in 2 out of 11 children, and biopsies were described as “mild superficial perivascular dermatitis” (10). In our series, 18 % of children (4 of 22) with COVID-19-related chilblains were also affected with EM-like lesions.

Infections, usually viral, are the most common cause of EM in children and adults (11). Among viruses, herpes simplex virus is most frequently found, followed by Epstein-Barr virus, varicella, adenovirus, cytomegalovirus and orf (11). Drugs are the second most common cause of EM and vaccines are an unusual cause (11). None of our patients had a recent history or clinical signs of any of these disorders or exposures.

A causal link of EM with COVID-19 in our patients is supported by the following features: 1) A positive SARS-CoV-2 PCR test in 1 patient; 2) A history of contact with a suspected COVID-19 case in one patient and mild respiratory symptoms some days before the skin lesions appeared in three; 3) Coincidence during the peak period of incidence of COVID-19 in Madrid; 4) The presence in the same patients of EM and chilblains, appearing during an outbreak in an epidemic setting; and 5) The positive immunohistochemistry for SARS-CoV/SARS-CoV-2 spike protein in the endothelia and eccrine epithelia in the 2 cases biopsied.

Despite the clinical diagnosis, histopathology failed to demonstrate the typical features of EM. Both cases showed variable degrees of interface dermatitis, without necrotic keratinocytes, and a deep extension of the inflammatory infiltrate extending into the subcutis with vasculopathic changes. Necrotic keratinocytes, which are commonly seen in EM biopsies, were not identified, and spongiosis was mild to moderate in our patients. Similarly, the deep extension of the inflammatory process to involve the deep vascular plexus and eccrine glands is not a feature of EM. However, the overall histopathological features are

similar to those found in chilblains, including those described during COVID-19 pandemic (7,9).

All four patients had an excellent outcome, without complications or severe disease involvement, and lesions eventually disappeared within 1-3 weeks of follow-up. Treatment with oral corticosteroids was well tolerated in one of them.

In conclusion, EM-like lesions may appear together with chilblains in adolescents in the setting of the COVID-19 pandemic. This coincidence and the positivity for SARS-CoV/SARS-CoV-2 spike protein by immunohistochemistry strongly suggest a link between EM-like lesions and SARS-CoV-2.

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Figure legends

Figure 1. A, B, Case 1. Large, confluent, targetoid lesions on the hands and elbows, with some small hemorrhagic crusts.

Figure 2. A, B, Case 2. Targetoid lesions on dorsum of hands and knees. C, Case 3. Targetoid lesions on the hands and forearms. Also, note pernioytic erythema on the fingertips.

Figure 3. A-C. Skin biopsy from the lateral foot in case 1. A, Interface dermatitis with superficial and deep perivascular lymphocytic inflammation (H&E, original magnification 20X). B, Moderate exocytosis with vacuolar changes and spongiosis. No necrotic keratinocytes are seen. (H&E stain, original magnification 100X). C, Deep extension of the inflammatory infiltrate involving eccrine glands (H&E stain, original magnification 40X). D-F. Skin biopsy from the knee in case 2. A, Superficial and deep perivascular inflammation and vascular ectasia (H&E stain, original magnification 20X). B, Mild exocytosis, vacuolar changes and spongiosis. No necrotic keratinocytes are seen. (H&E stain, original magnification 40X). C, A mid dermal vessel showing transmural lymphocytic infiltration and plump endothelial lining (H&E stain, original magnification 400X).

Figure 4. Case 1. Cytoplasmic granular positivity for SARS-CoV/SARS-CoV-2 spike protein in endothelial cells of the upper dermis vessels (A, B). and epithelial cells of the acrosyringia (C) (original magnification A: 100X; B: 200X; C:400X).

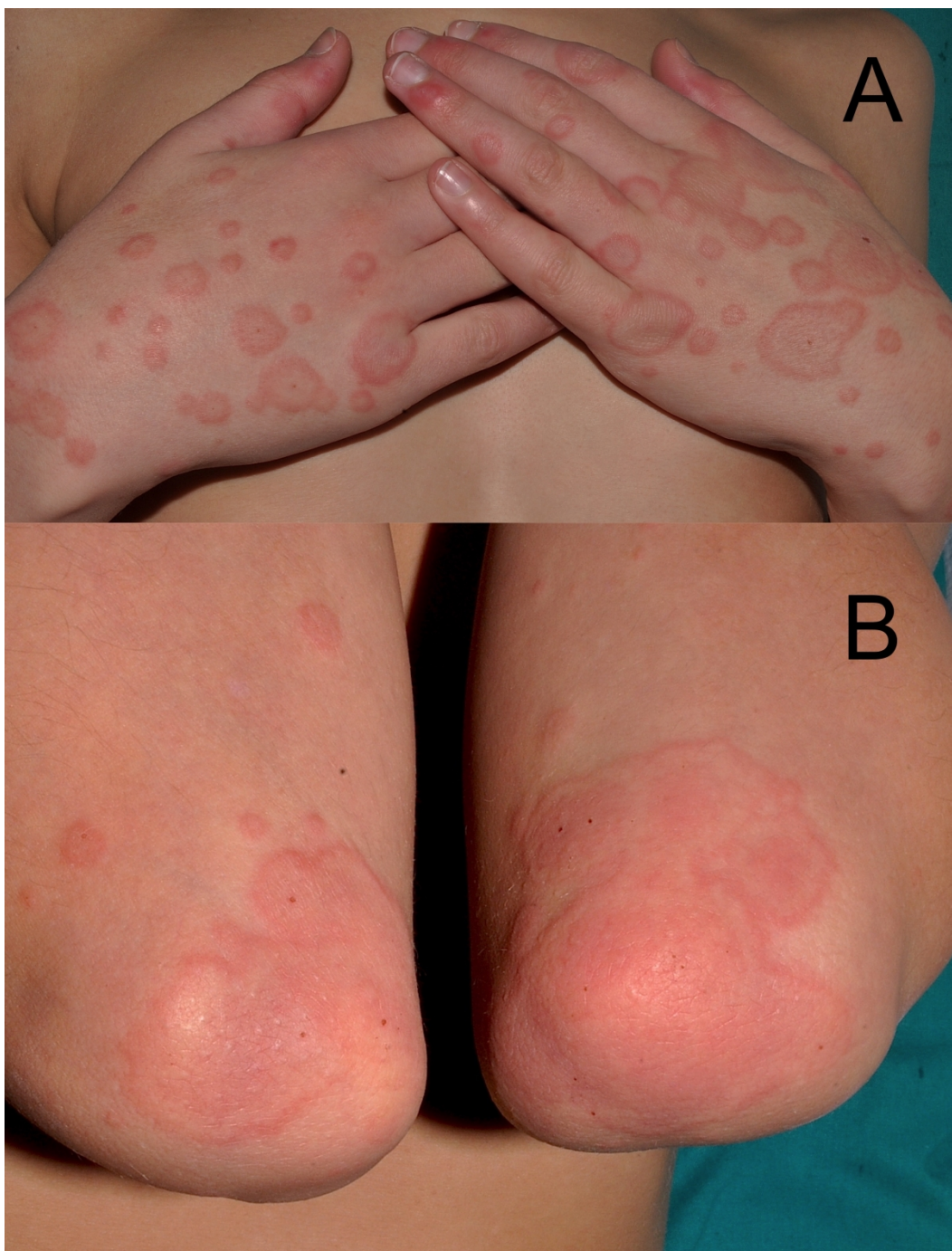
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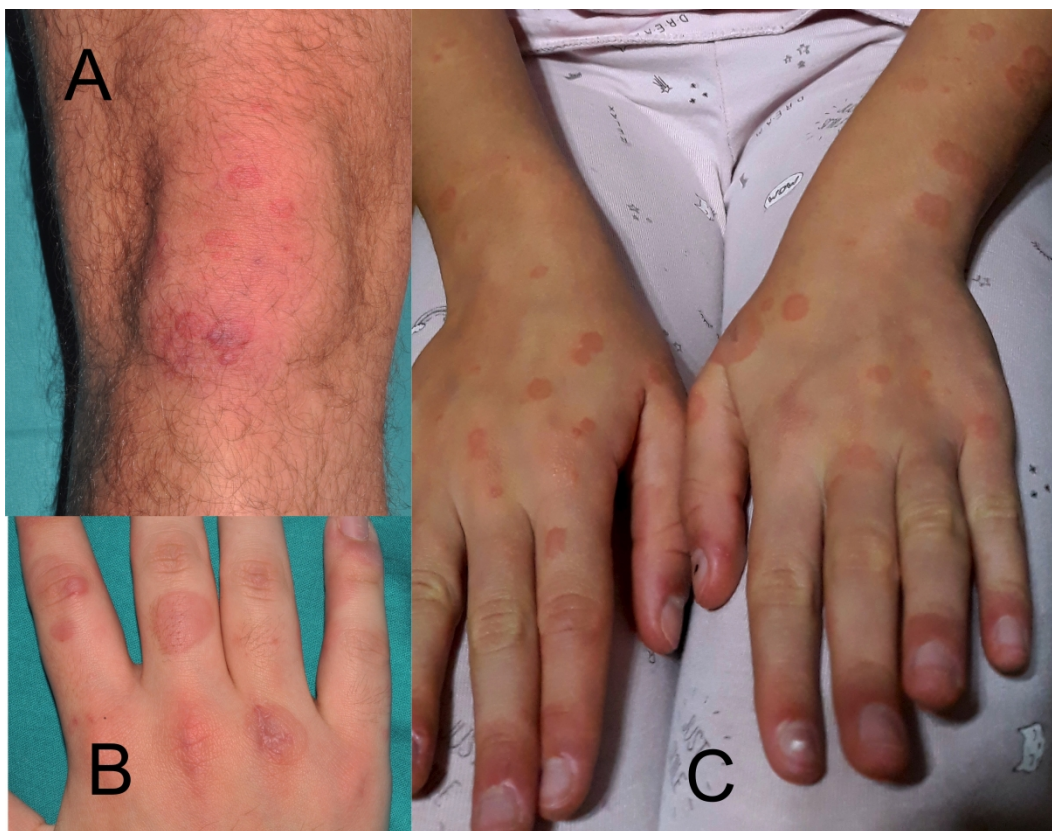
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Table. Summary of clinical features of 4 patients with erythema multiforme

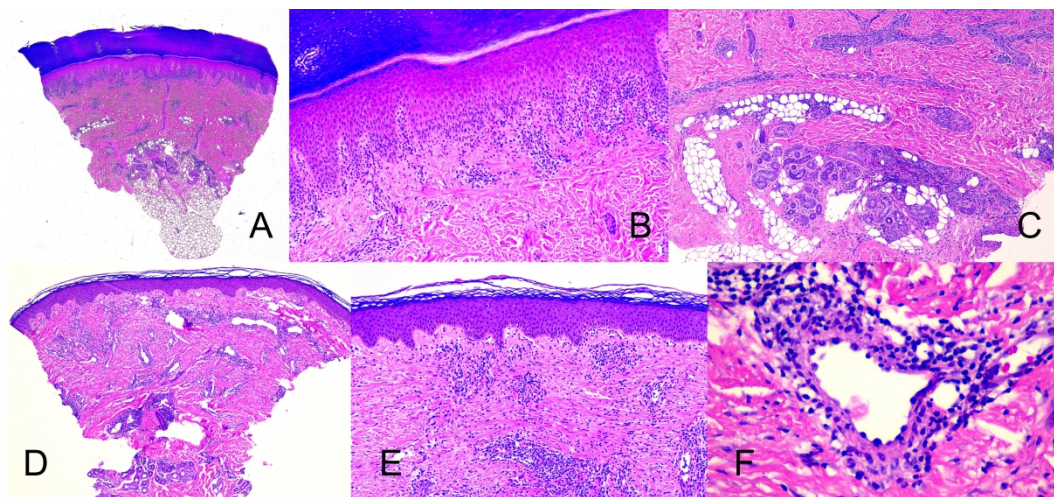
Case	Sex	Age	Site of involvement	Local symptoms	Systemic symptoms	Household contacts	Lab analyses	PCR	Comments
1	M	12 y	Elbows, knees, forearms, ankles, dorsal and lateral feet, hands, ears	Pruritus	None	None	Not done	-	Biopsy taken Topical corticosteroids used Complete recovery
2	M	17 y	Elbows, knees, dorsal feet, hands	Pruritus	Mild respiratory symptoms	Yes (suspected COVID-19)	Coagulation and D-dimer normal	-	Biopsy taken Oral corticosteroids used Complete recovery
3	F	11 y	Elbows, knees, thighs, arms, forearms, legs, ankles, dorsal feet, dorsal hands	None	Mild GI symptoms	None	Hemogram and coagulation normal	+	No treatment Complete recovery
4	M	15 y	Elbows, knees, forearms, ankles, dorsal feet, hands	Pruritus and pain	Mild respiratory symptoms	None	Hemogram, coagulation and D-dimer normal	-	No treatment Complete recovery



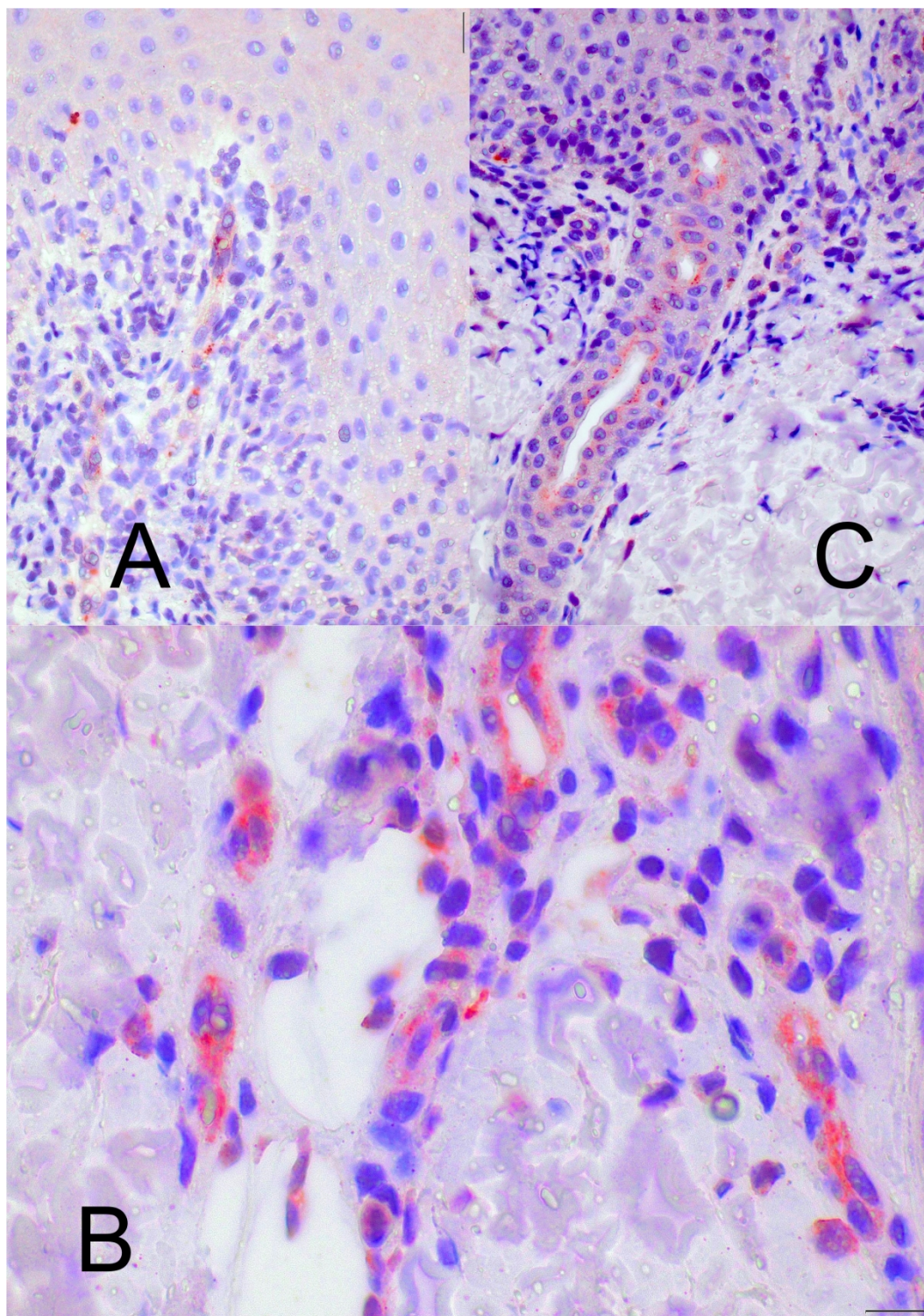
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